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Thrombin-receptor antagonist vorapaxar in acute coronary syndromes

Tricoci, Pierluigi ; Huang, Zhen ; Held, Claes ; et al

Abstract: BACKGROUND: Vorapaxar is a new oral protease-activated-receptor 1 (PAR-1) antagonist that inhibits thrombin-induced platelet activation. METHODS: In this multinational, double-blind, randomized trial, we compared vorapaxar with placebo in 12,944 patients who had acute coronary syndromes without ST-segment elevation. The primary end point was a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization. RESULTS: Follow-up in the trial was terminated early after a safety review. After a median follow-up of 502 days (interquartile range, 349 to 667), the primary end point occurred in 1031 of 6473 patients receiving vorapaxar versus 1102 of 6471 patients receiving placebo (Kaplan-Meier 2-year rate, 18.5% vs. 19.9%; hazard ratio, 0.92; 95% confidence interval [CI], 0.85 to 1.01; P=0.07). A composite of death from cardiovascular causes, myocardial infarction, or stroke occurred in 822 patients in the vorapaxar group versus 910 in the placebo group (14.7% and 16.4%, respectively; hazard ratio, 0.89; 95% CI, 0.81 to 0.98; P=0.02). Rates of moderate and severe bleeding were 7.2% in the vorapaxar group and 5.2% in the placebo group (hazard ratio, 1.35; 95% CI, 1.16 to 1.58; P<0.001). Intracranial hemorrhage rates were 1.1% and 0.2%, respectively (hazard ratio, 3.39; 95% CI, 1.78 to 6.45; P<0.001). Rates of nonhemorrhagic adverse events were similar in the two groups. CONCLUSIONS: In patients with acute coronary syndromes, the addition of vorapaxar to standard therapy did not significantly reduce the primary composite end point but significantly increased the risk of major bleeding, including intracranial hemorrhage. (Funded by Merck; TRACER ClinicalTrials.gov number, NCT00527943.).

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ORIGINAL ARTICLE

Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes

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ABSTRACT

BACKGROUND

Vorapaxar is a new oral protease-activated-receptor 1 (PAR-1) antagonist that inhibits thrombin-induced platelet activation.

METHODS

In this multinational, double-blind, randomized trial, we compared vorapaxar with placebo in 12,944 patients who had acute coronary syndromes without ST-segment elevation. The primary end point was a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization.

RESULTS

Follow-up in the trial was terminated early after a safety review. After a median follow-up of 502 days (interquartile range, 349 to 667), the primary end point occurred in 1031 of 6473 patients receiving vorapaxar versus 1102 of 6471 patients receiving placebo (Kaplan–Meier 2-year rate, 18.5% vs. 19.9%; hazard ratio, 0.92; 95% confidence interval [CI], 0.85 to 1.01; $P=0.07$). A composite of death from cardiovascular causes, myocardial infarction, or stroke occurred in 822 patients in the vorapaxar group versus 910 in the placebo group (14.7% and 16.4%, respectively; hazard ratio, 0.89; 95% CI, 0.81 to 0.98; $P=0.02$). Rates of moderate and severe bleeding were 7.2% in the vorapaxar group and 5.2% in the placebo group (hazard ratio, 1.35; 95% CI, 1.16 to 1.58; $P<0.001$). Intracranial hemorrhage rates were 1.1% and 0.2%, respectively (hazard ratio, 3.39; 95% CI, 1.78 to 6.45; $P<0.001$). Rates of nonhemorrhagic adverse events were similar in the two groups.

CONCLUSIONS

In patients with acute coronary syndromes, the addition of vorapaxar to standard therapy did not significantly reduce the primary composite end point but significantly increased the risk of major bleeding, including intracranial hemorrhage. (Funded by Merck; TRACER ClinicalTrials.gov number, NCT00527943.)

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THE RISK OF RECURRENT ISCHEMIC complications among patients with acute coronary syndromes without ST-segment elevation remains high despite contemporary treatment strategies, including the use of early revascularization and dual antiplatelet therapy.^{1,2} Hence, the assessment of new platelet inhibitors has continued to be an important avenue of investigation.³⁻⁵

Thrombin activates platelets through two protease-activated receptors (PARs), PAR-1 and PAR-4.⁶ PAR-1 is activated by lower concentrations of thrombin than PAR-4 and mediates a more rapid platelet-activation response.⁷ In pre-clinical models, selective PAR-1 blockade resulted in potent inhibition of thrombin-induced platelet aggregation but appeared to preserve primary hemostatic function.⁸

Vorapaxar (SCH 530348, Merck) is an oral competitive PAR-1 antagonist that inhibits thrombin-induced platelet aggregation. In two phase 2 trials involving patients undergoing elective percutaneous coronary intervention (PCI) and in those with acute coronary syndromes without ST-segment elevation receiving dual antiplatelet therapy, vorapaxar (with loading doses up to 40 mg and maintenance doses up to 2.5 mg) did not significantly increase the risk of bleeding as compared with placebo, whereas a trend toward fewer myocardial infarctions was observed.^{9,10} We conducted a multinational, randomized, double-blind, placebo-controlled study, the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial, to determine whether the addition of vorapaxar to standard therapy would be superior to placebo in reducing recurrent ischemic cardiovascular events and to determine its safety profile in patients with acute coronary syndromes without ST-segment elevation.

METHODS

STUDY DESIGN AND ORGANIZATION

Details of the study design and organization have been published previously.¹¹ The trial was funded by Merck. A consortium of international academic research organizations, led by the Duke Clinical Research Institute in collaboration with the sponsor, designed and conducted the study, collected the data, and performed the analyses.¹² An academically led executive committee supervised the trial design and operations (see the Supplementary Appendix, available with the full

text of this article at NEJM.org). The study protocol is also available at NEJM.org. The steering committee consisted of representatives from all participating countries. Analyses presented in this article were performed independently at the Duke Clinical Research Institute with the use of the raw data. The first author drafted the manuscript, and all the authors contributed to its revision. The study was approved by the appropriate national and institutional regulatory authorities and ethics committees. The executive committee made the decision to submit the manuscript for publication.

STUDY PARTICIPANTS

Patients were eligible if they had had acute symptoms of coronary ischemia within 24 hours before hospital presentation and at least one of the following findings: a cardiac troponin (I or T) or creatine kinase MB (CK-MB) level that was higher than the upper limit of the normal range or new ST-segment depression of more than 0.1 mV or transient ST-segment elevation (<30 minutes) of more than 0.1 mV in at least two contiguous leads. Also required were one or more of the following four criteria: an age of at least 55 years; previous myocardial infarction, PCI, or coronary-artery bypass grafting (CABG); diabetes mellitus; or peripheral arterial disease. A complete list of inclusion and exclusion criteria is provided in the Supplementary Appendix. All patients provided written informed consent.

STUDY PROCEDURES

Patients were randomly assigned in a 1:1 ratio to receive vorapaxar (at a loading dose of 40 mg and a daily maintenance dose of 2.5 mg thereafter) or matching placebo with stratification according to the intention to use a glycoprotein IIb/IIIa inhibitor (vs. none) and the intention to use a parenteral direct thrombin inhibitor (vs. other anti-thrombin agents). Study-group assignment was performed with the use of a 24-hour automated voice-response system. The loading dose was to be given immediately after randomization and at least 1 hour before any coronary revascularization procedure. The maintenance dose was to be continued for the entire duration of the study, with a planned minimum of 1 year. Investigators were encouraged to follow current practice guidelines of professional societies.^{1,2} Therefore, it was anticipated that the majority of patients

would be treated with a combination of aspirin and a P2Y₁₂ inhibitor.

Follow-up assessment was performed during the index hospitalization and at 1 month, 4 months, 8 months, 12 months, and every 6 months thereafter. A final visit was scheduled at the end of the study. Patients who prematurely discontinued treatment were followed by telephone at the same intervals. The recruitment period began on December 18, 2007, and ended on June 4, 2010. In selected centers participating in a substudy of pharmacokinetics and pharmacodynamics and in China, an additional 340 patients were recruited up to November 30, 2010, to achieve enrollment goals.

Follow-up of these patients was to be completed simultaneously with that of the main cohort.

END POINTS

The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with re-hospitalization, or urgent coronary revascularization. The prespecified key secondary end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke. Other efficacy end points were exploratory. The main safety end points were a composite of moderate or severe bleeding according to the Global

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Placebo (N = 6471)	Vorapaxar (N = 6473)
Age		
Median — yr	64.0	64.0
Interquartile range — yr	58.0–72.0	58.0–71.0
≥75 yr — no. (%)	1096 (16.9)	1110 (17.1)
Female sex — no. (%)	1822 (28.2)	1810 (28.0)
Race or ethnic group — no./total no. (%)†		
White	5510/6453 (85.4)	5529/6456 (85.6)
Black	161/6453 (2.5)	151/6456 (2.3)
Asian	533/6453 (8.3)	523/6456 (8.1)
Other	249/6453 (3.9)	253/6456 (3.9)
Body weight — kg		
Median	80.0	80.4
Interquartile range	70.0–92.0	70.0–93.0
Region of enrollment — no. (%)		
North America	1694 (26.2)	1710 (26.4)
South America	420 (6.5)	428 (6.6)
Western Europe	2930 (45.3)	2909 (44.9)
Eastern Europe	742 (11.5)	745 (11.5)
Asia	474 (7.3)	462 (7.1)
Australia or New Zealand	211 (3.3)	219 (3.4)
Cardiovascular risk factors — no./total no. (%)		
Hypertension	4591/6469 (71.0)	4537/6470 (70.1)
Hyperlipidemia	4024/6469 (62.2)	4038/6470 (62.4)
Diabetes mellitus	2030/6469 (31.4)	2040/6470 (31.5)
Current tobacco use	1787/6469 (27.6)	1749/6470 (27.0)
Creatinine clearance — no./total no. (%)		
<30 ml/min	88/6120 (1.4)	102/6141 (1.7)
30–60 ml/min	743/6120 (12.1)	734/6141 (12.0)

Table 1. (Continued.)

Characteristic	Placebo (N = 6471)	Vorapaxar (N = 6473)
Cardiovascular disease history — no./total no. (%)		
Myocardial infarction	1890/6469 (29.2)	1901/6470 (29.4)
PCI	1531/6467 (23.7)	1559/6467 (24.1)
CABG	766/6467 (11.8)	777/6467 (12.0)
Stroke	262/6469 (4.1)	291/6470 (4.5)
Peripheral arterial disease	468/6469 (7.2)	468/6470 (7.2)
Positive for troponin or creatine kinase MB — no./total no. (%)	6037/6429 (93.9)	6013/6428 (93.5)
Electrocardiographic findings — no. (%)		
ST-segment depression	2122 (32.8)	2077 (32.1)
ST-segment elevation†	378 (5.8)	358 (5.5)
TIMI risk score — no. (%)§		
0–2	27 (0.4)	40 (0.6)
3–4	3357 (51.9)	3341 (51.6)
5–7	3087 (47.7)	3092 (47.8)
Killip class — no./total no. (%)¶		
II	260/6415 (4.1)	234/6417 (3.6)
III or IV	61/6415 (1.0)	69/6417 (1.1)
Stratification factor — no. (%)		
Intention to use glycoprotein IIb/IIIa inhibitor	1345 (20.8)	1365 (21.1)
Intention to use direct thrombin inhibitor	1098 (17.0)	1058 (16.3)
Use of antiplatelet drugs — no./total no. (%)		
Thienopyridine	5639/6471 (87.1)	5668/6473 (87.6)
Aspirin	6272/6471 (96.9)	6243/6473 (96.4)
≤100 mg	3778/6272 (60.2)	3745/6243 (60.0)
>100 mg	2494/6272 (39.8)	2498/6243 (40.0)

* There were no significant differences between the groups. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

† Race or ethnic group was reported by investigators after interviews with patients.

‡ Patients with transient (<30 min) ST-segment elevation were eligible.

§ The Thrombolysis in Myocardial Infarction (TIMI) risk score ranges from 0 to 7, with higher scores indicating greater risk.

¶ According to the Killip classification, class II indicates cardiac S3 or rales on 50% or less of the lung fields, class III indicates rales on more than 50% of the lung fields, and class IV indicates signs of cardiogenic shock.

Use of Strategies to Open Occluded Coronary Arteries (GUSTO) classification and clinically significant bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) classification, defined as TIMI major or minor bleeding or bleeding that required unplanned medical or surgical treatment or laboratory evaluation.^{13,14} End-point definitions are provided in the Supplementary Appendix. A central clinical-events committee, whose members were unaware of the study-group assignments, assessed all suspected efficacy and bleeding events.

STATISTICAL ANALYSIS

The primary hypothesis was that vorapaxar would be superior to standard therapy alone for the prevention of cardiac ischemic events. The trial was prospectively designed and powered to detect significant differences in both the primary end point and the key secondary end point. To account for multiplicity, the primary end point and the key secondary end point were tested in sequence. If superiority was not achieved for the primary end point, it could not be declared for the key secondary end point. After an interim

assessment of aggregated event rates, and after approximately 6500 subjects had been enrolled, the planned sample size was increased from 10,000 to approximately 12,500 patients. We calculated that a minimum of 1900 primary end-point events would provide a power of more than 95% to detect a 15% hazard reduction in the vorapaxar group, as compared with the placebo group, and 1457 key secondary end-point events would provide a power of 90% to detect a 15% hazard reduction.

Efficacy analyses were performed according to study-group assignments on the basis of the time to the first occurrence of any component of the composite end points. Estimates of the hazard ratios and 95% confidence intervals for vorapaxar as compared with placebo were calculated with the use of a Cox proportional-hazards model in which study-group assignment and stratification factors were included as covariates. Patients were followed until the final visit or the last assessment of end points.

A planned formal interim analysis was performed on June 25, 2010, which resulted in the

continuation of the study as planned. To account for the formal interim analysis, the significance level was adjusted on the basis of the O'Brien–Fleming method. A significance level of 0.049 was used for the analysis of the primary and key secondary efficacy end points at the end of the study. The safety analyses, which included patients who received at least one dose of a study drug, were performed with the use of a Cox model for the period in which the study drug was received. Event rates are presented as 2-year Kaplan–Meier estimates, unless otherwise specified. Continuous data are provided as medians with interquartile ranges. The statistical analysis plan is available at NEJM.org.

RESULTS

STUDY PARTICIPANTS AND FOLLOW-UP

A total of 12,944 patients at 818 sites in 37 countries were enrolled. After an unplanned safety review on January 8, 2011, the data and safety monitoring board recommended that the trial be stopped rather than continue as planned until

Table 2. Treatment during Index Hospitalization.

Variable	Placebo (N=6471)	Vorapaxar (N=6473)
Time from symptom onset to randomization — hr		
Median	26.9	26.7
Interquartile range	7.6–50.2	17.6–48.7
Time from arrival at hospital to randomization — hr		
Median	21.1	21.2
Interquartile range	12.2–41.1	12.2–40.6
Time from randomization to first dose of study drug — min		
Median	21.0	21.0
Interquartile range	10.0–42.0	10.0–43.0
Receipt of randomized treatment — no. (%)	6441 (99.5)	6446 (99.6)
Discontinuation before the end of the study or death — no./total no. (%)	1726/6441 (26.8)	1818/6446 (28.2)
Adverse event	489/1726 (28.3)	649/1818 (35.7)
Reason unrelated to assigned study treatment	865/1726 (50.1)	858/1818 (47.2)
Noncompliance with protocol	287/1726 (16.6)	232/1818 (12.8)
Did not have disease of interest	65/1726 (3.8)	56/1818 (3.1)
Unknown reason	20/1726 (1.2)	23/1818 (1.3)
Exposure to randomized treatment — days		
Median	393.0	379.0
Interquartile range	236.0–588.0	231.0–585.0

Table 2. (Continued.)

Variable	Placebo (N = 6471)	Vorapaxar (N = 6473)
Cardiac catheterization — no./total no. (%)	5689/6471 (87.9)	5710/6473 (88.2)
PCI — no./total no. (%)		
Any	3715/6471 (57.4)	3764/6473 (58.1)
Performed ≤24 hr after randomization	2929/3715 (78.8)	2982/3764 (79.2)
Stenting during index PCI — no./total no. (%)		
Any	3526/3715 (94.9)	3549/3764 (94.3)
Drug-eluting stent	2042/3526 (57.9)	1973/3549 (55.6)
Bare-metal stent	1636/3526 (46.4)	1732/3549 (48.8)
Interval between administration of loading dose of study drug and PCI — hr		
Median	3.5	3.5
Interquartile range	1.8–20.8	1.8–20.6
CABG		
Any — no. (%)	673 (10.4)	639 (9.9)
Interval between administration of loading dose of study drug and CABG — hr		
Median	118.9	120.0
Interquartile range	48.0–214.4	47.3–194.1
Discontinuation of study drug before CABG — no./total no. (%)	153/673 (22.7)	165/639 (25.8)
Antiplatelet use — no. (%)		
Clopidogrel	5933 (91.7)	5950 (91.9)
Aspirin	6415 (99.1)	6410 (99.0)
Glycoprotein IIb/IIIa inhibitor	1349 (20.8)	1352 (20.9)

June 4, 2011. The protocol-defined target number of primary efficacy end points had been reached. In addition, the board recommended termination of study medication in patients with a history of stroke who had been enrolled in an independent companion trial involving patients with chronic vascular disease.¹⁵ On January 13, 2011, sites were notified that they should tell all patients to stop taking the assigned study drug and schedule a final visit.

Baseline demographic characteristics were well balanced between the two study groups (Table 1). The median follow-up period was 502 days (interquartile range, 349 to 667) (see the Supplementary Appendix). A total of 761 patients (5.9%) declined to continue participation during follow-up. This group included patients who withdrew their consent to any trial assessment, those who agreed to be contacted at the end of the study for a vital-status assessment, and those who were

lost to follow-up. Within this group, vital status was assessed in 512 patients at the end of the study. Overall, only 15 patients (0.1%) were lost to follow-up (see the Supplementary Appendix).

STUDY DRUG AND CONCOMITANT THERAPIES

Patients underwent randomization a median of 21.2 hours (interquartile range, 12.2 to 40.8) after hospitalization (Table 2). The median exposure to a study drug was 386 days (interquartile range, 233 to 586). Rates of study-drug discontinuation were slightly higher in the vorapaxar group than in the placebo group (28.2% vs. 26.8%).

Clopidogrel was administered in 91.8% of patients during the index hospitalization, and cardiac catheterization was performed in 88.1% of patients, PCI in 57.8%, and CABG in 10.1% (Table 2). The loading dose of the assigned study drug was given a median of 3.5 hours (interquartile range, 1.8 to 20.7) before PCI.

PRIMARY AND KEY SECONDARY END POINTS

One of the components of the primary end point (a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) occurred in 1031 of 6473 patients in the vorapaxar group and in 1102 of 6471 patients in the placebo group, corresponding to a 2-year rate of 18.5% in the vorapaxar group and 19.9% in the placebo group (hazard ratio in the vorapaxar group, 0.92; 95% confidence interval [CI], 0.85 to 1.01; $P=0.07$) (Fig. 1A and Table 3).

The key secondary end point (a composite of death from cardiovascular causes, myocardial infarction, or stroke) occurred in 822 patients in the vorapaxar group and 910 patients in the placebo group, for 2-year Kaplan–Meier estimates of 14.7% and 16.4%, respectively (hazard ratio, 0.89; 95% CI, 0.81 to 0.98; $P=0.02$) (Fig. 1B and Table 3). Among the individual components of the efficacy end points, the reduction in the rate of myocardial infarction was the main effect observed in the vorapaxar group, as compared with the placebo group (11.1% vs. 12.5% at 2 years; hazard ratio, 0.88; 95% CI, 0.79 to 0.98; $P=0.02$). A reduction in the rate of type 1 (spontaneous) myocardial infarction¹⁶ in the vorapaxar group largely accounted for the difference (5.6% vs. 6.8%).

OTHER EFFICACY END POINTS

The composite end point of death from cardiovascular causes or myocardial infarction also occurred less frequently in the vorapaxar group than in the placebo group (13.5% vs. 14.9%; hazard ratio, 0.90; 95% CI, 0.81 to 0.99; $P=0.03$) (Table 3). The rates of death from any cause were 6.5% in the vorapaxar group and 6.1% in the placebo group (hazard ratio, 1.05; 95% CI, 0.90 to 1.23; $P=0.52$).

Among patients who underwent placement of a stent during the index hospitalization, the rates of definite or probable stent thrombosis were similar in the two groups: 1.7% in the vorapaxar group and 1.5% in the placebo group (hazard ratio, 1.12; 95% CI, 0.78 to 1.62; $P=0.54$). Overall, stroke rates were similar in the two groups. However, the 2-year rate of ischemic stroke was lower in the vorapaxar group (1.1%) than in the placebo group (1.4%), whereas the rate of hemorrhagic stroke was higher in the vorapaxar group (0.3%) than in the placebo group (0.1%).

BLEEDING OUTCOMES

Vorapaxar increased the rate of GUSTO moderate or severe bleeding, as compared with placebo (7.2% vs. 5.2%; hazard ratio, 1.35; 95% CI, 1.16 to 1.58; $P<0.001$) (Table 4 and Fig. 2A). The rate of clinically significant TIMI bleeding was increased among patients treated with vorapaxar (20.2% vs. 14.6%; hazard ratio, 1.43; 95% CI, 1.31 to 1.57; $P<0.001$) (Table 4 and Fig. 2B). The excess bleeding events continued to accrue during follow-up. The vorapaxar group also had higher rates of GUSTO severe bleeding (2.9% vs. 1.6%; hazard ratio, 1.66; 95% CI, 1.27 to 2.16; $P<0.001$), TIMI major bleeding (4.0% vs. 2.5%; hazard ratio, 1.53; 95% CI, 1.24 to 1.90; $P<0.001$), and intracranial hemorrhage (1.1% vs. 0.2%; hazard ratio, 3.39; 95% CI, 1.78 to 6.45; $P<0.001$), with an incremental risk over time (Table 4 and the Supplementary Appendix). Rates of CABG-related bleeding during the index hospitalization did not differ significantly between the two study groups, and rates of reoperation for bleeding and fatal bleeding were similar.

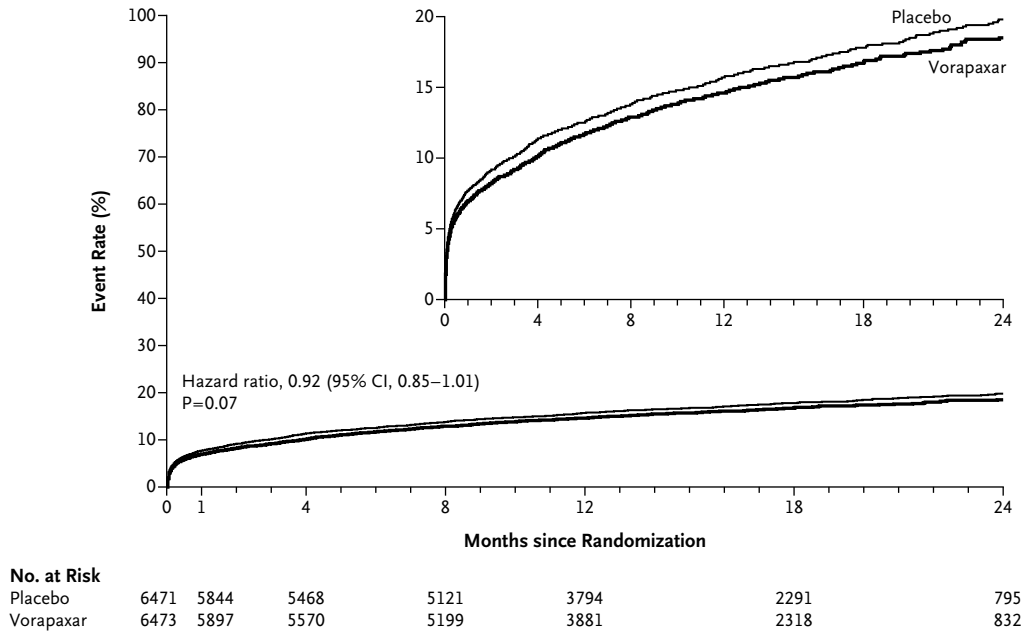
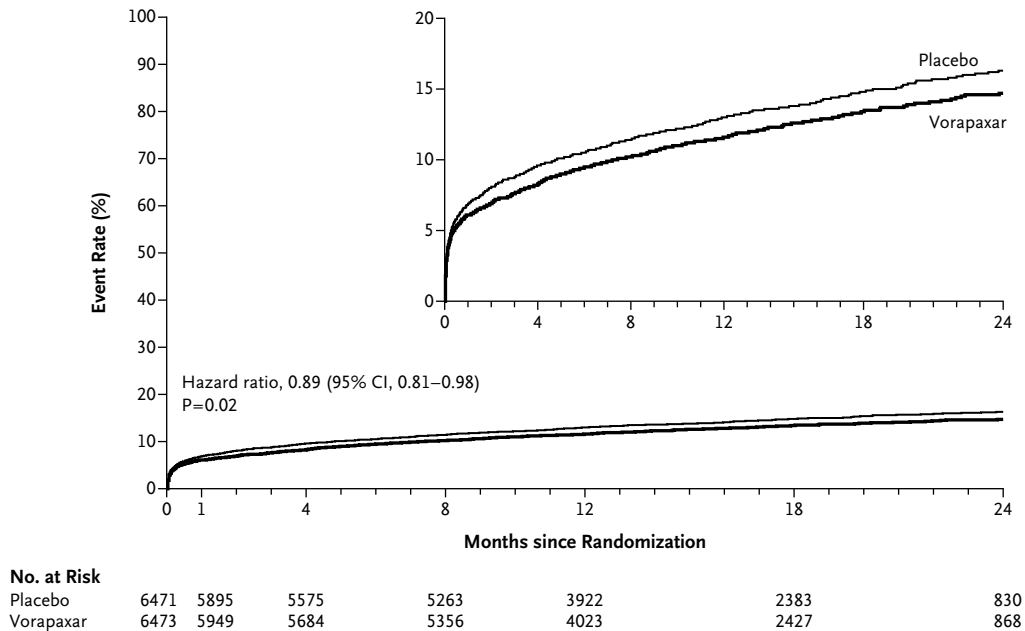
SUBGROUP ANALYSES

Primary and key secondary efficacy outcomes were consistent across subgroups (see the Supplementary Appendix). A trend toward more pronounced efficacy with vorapaxar was observed for both the primary and key secondary end points in patients who were not treated with thienopyridine at randomization.

Vorapaxar increased rates of bleeding in most subgroups (see the Supplementary Appendix). Patients with lower body weight who received vorapaxar had a higher risk of GUSTO moderate or severe bleeding than did patients with higher body weight ($P=0.03$ for interaction). The hazard of GUSTO moderate or severe bleeding in the vorapaxar group was not increased in patients who were not receiving a thienopyridine at randomization, whereas the risk was increased in patients who were receiving a thienopyridine (hazard ratio, 0.95; 95% CI, 0.65 to 1.40 with no thienopyridine; hazard ratio, 1.45; 95% CI, 1.23 to 1.71 with thienopyridine; $P=0.04$ for interaction).

DISCUSSION

In previous studies, simultaneous inhibition of two pathways of platelet activation has been shown to reduce the occurrence of recurrent ischemic

A Primary End Point**B Key Secondary End Point****Figure 1. Study End Points.**

Shown are Kaplan–Meier event rates at 2 years in the two study groups for the primary efficacy end point (a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) (Panel A) and the key secondary efficacy end point (a composite of death from cardiovascular causes, myocardial infarction, or stroke) (Panel B).

Table 3. Efficacy End Points.*

End Point	Placebo (N=6471)		Vorapaxar (N=6473)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate at 2 Yr†	Patients with Event	Event Rate at 2 Yr†		
	no./total no. (%)	% (95% CI)	no./total no. (%)	% (95% CI)		
Primary efficacy end point	1102/6471 (17.0)	19.9 (18.7–21.1)	1031/6473 (15.9)	18.5 (17.4–19.7)	0.92 (0.85–1.01)	0.07
Key secondary efficacy end point	910/6471 (14.1)	16.4 (15.3–17.5)	822/6473 (12.7)	14.7 (13.7–15.7)	0.89 (0.81–0.98)	0.02
Other secondary end points						
Composite of death from cardiovascular causes or myocardial infarction	834/6471 (12.9)	14.9 (13.9–16.0)	755/6473 (11.7)	13.5 (12.5–14.5)	0.90 (0.81–0.99)	0.03
Death from cardiovascular causes	207/6471 (3.2)	3.8 (3.2–4.3)	208/6473 (3.2)	3.8 (3.3–4.4)	1.00 (0.83–1.22)	0.96
Myocardial infarction	698/6471 (10.8)	12.5 (11.6–13.5)	621 (9.6)	11.1 (10.2–12.0)	0.88 (0.79–0.98)	0.02
Type of myocardial infarction						
Type 1, spontaneous	440/6471 (6.8)		365/6473 (5.6)			
Type 2, secondary	24/6471 (0.4)		35/6473 (0.5)			
Type 3, with sudden death	2/6471 (<0.1)		0/6473			
Type 4a, associated with PCI	180/6471 (2.8)		163/6473 (2.5)			
Type 4b, associated with stent thrombosis	40/6471 (0.6)		36/6473 (0.6)			
Type 5, associated with CABG	12/6471 (0.2)		20/6473 (0.3)			
Stroke						
Any	103/6471 (1.6)	2.1 (1.7–2.6)	96/6473 (1.5)	1.9 (1.5–2.3)	0.93 (0.70–1.23)	0.61
Ischemic	93/6471 (1.4)		74/6473 (1.1)		0.79 (0.59–1.08)	0.14
Hemorrhagic	8/6471 (0.1)		22/6473 (0.3)		2.73 (1.22–6.14)	0.02
Urgent coronary revascularization	189/6471 (2.9)	3.5 (3.0–4.0)	203/6473 (3.1)	3.8 (3.2–4.4)	1.07 (0.88–1.31)	0.49
Recurrent ischemia with rehospitalization	69/6471 (1.1)	1.5 (1.1–1.9)	79/6473 (1.2)	1.6 (1.2–2.1)	1.14 (0.83–1.58)	0.42
Death from any cause	318/6471 (4.9)	6.1 (5.4–6.8)	334/6473 (5.2)	6.5 (5.8–7.3)	1.05 (0.90–1.23)	0.52
Stent thrombosis per Academic Research Consortium definition						
Definite or probable	54/3526 (1.5)		61/3549 (1.7)		1.12 (0.78–1.62)	0.54
Definite	47/3526 (1.3)		50/3549 (1.4)			
Probable	7/3526 (0.2)		11/3549 (0.3)			

* The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization. The prespecified key secondary end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke.

† Event rates at 2 years were calculated with the use of the Kaplan–Meier method.

events in patients with acute coronary syndromes but to increase the risk of bleeding complications.^{3–5,17} In our study, the addition of PAR-1 inhibition with vorapaxar to standard therapy resulted in a nonsignificant relative reduction of 8% in the primary end point. Vorapaxar reduced the hazard of the key secondary end point (death from cardiovascular causes, myocardial infarction, or stroke) by 11%, with the 95% confidence interval

excluding a null effect. However, a hierarchical statistical-testing strategy was used to control for multiple comparisons, and since superiority with respect to the primary end point was not achieved, superiority with respect to the key secondary end point cannot be declared.

The difference in the rates of the composite end points was driven by a reduction in the rate of myocardial infarction, in particular type 1

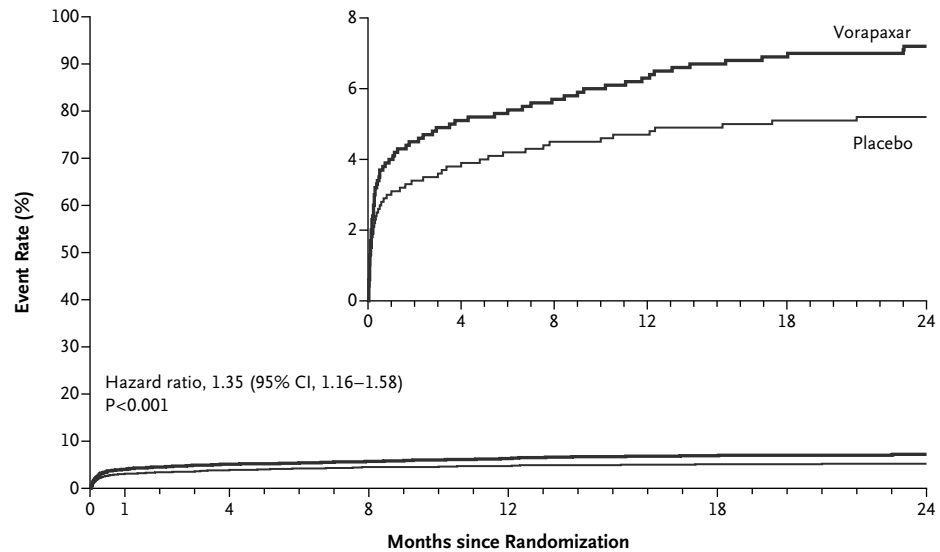
Table 4. Bleeding End Points in the As-Treated Population.*

End Point	Placebo (N=6441)		Vorapaxar (N=6446)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate at 2 Yr†	Patients with Event	Event Rate at 2 Yr†		
	no./total no. (%)	% (95% CI)	no./total no. (%)	% (95% CI)		
GUSTO criteria						
Moderate or severe bleeding	290/6441 (4.5)	5.2 (4.6–5.9)	391/6446 (6.1)	7.2 (6.5–8.0)	1.35 (1.16–1.58)	<0.001
Severe bleeding	87/6441 (1.4)	1.6 (1.3–2.0)	144/6446 (2.2)	2.9 (2.3–3.4)	1.66 (1.27–2.16)	<0.001
TIMI criteria						
Clinically significant bleeding	755/6441 (11.7)	14.6 (13.5–15.7)	1065/6446 (16.5)	20.2 (19.0–21.4)	1.43 (1.31–1.57)	<0.001
Major bleeding	136/6441 (2.1)	2.5 (2.1–3.0)	208/6446 (3.2)	4.0 (3.4–4.6)	1.53 (1.24–1.90)	<0.001
Major or minor bleeding	217/6441 (3.4)	4.0 (3.4–4.6)	337/6446 (5.2)	6.5 (5.8–7.3)	1.56 (1.32–1.85)	<0.001
Non-CABG major or minor bleeding	153/6441 (2.4)	2.8 (2.4–3.3)	262/6446 (4.1)	5.3 (4.6–6.1)	1.72 (1.41–2.10)	<0.001
Non-CABG major bleeding	71/6441 (1.1)	1.3 (1.0–1.7)	131/6446 (2.0)	2.7 (2.2–3.3)	1.85 (1.39–2.47)	<0.001
Bleeding not meeting any TIMI definition	743/6441 (11.5)	14.5 (13.3–15.6)	982/6446 (15.2)	18.7 (17.5–19.9)	1.35 (1.23–1.48)	<0.001
Bleeding requiring medical attention	564/6441 (8.8)	11.2 (10.2–12.2)	784/6446 (12.2)	15.2 (14.1–16.3)	1.41 (1.26–1.57)	<0.001
Fatal bleeding	8/6441 (0.1)	0.2 (0.1–0.3)	15/6446 (0.2)	0.4 (0.2–0.5)	1.89 (0.80–4.45)	0.15
Intracranial hemorrhage	12/6441 (0.2)	0.2 (0.1–0.4)	40/6446 (0.6)	1.1 (0.7–1.5)	3.39 (1.78–6.45)	<0.001
Location						
Subdural	4/6441 (<0.1)		14/6446 (0.2)			
Intraparenchymal	7/6441 (0.1)		19/6446 (0.3)			
Subarachnoid	0/6441		4/6446 (<0.1)			
Unknown	1/6441 (<0.1)		3/6446 (<0.1)			
Cause						
Spontaneous	6/6441 (<0.1)		21/6446 (0.3)			
Traumatic	3/6441 (<0.1)		15/6446 (0.2)			
Related to surgery or other procedure	1/6441 (<0.1)		3/6446 (<0.1)			
Other	2/6441 (<0.1)		1/6446 (<0.1)			
Outcome						
Fatal	3/6441 (<0.1)		10/6446 (0.2)			
Nonfatal	8/6441 (0.1)		28/6446 (0.4)			
Contributing to death	1/6441 (<0.1)		2/6446 (<0.1)			
Index CABG-related bleeding‡						
TIMI major	49/671 (7.3)		62/639 (9.7)		1.34 (0.92–1.95)	0.13
Fatal bleeding	2/671 (0.3)		0/639			
Reoperation for bleeding	31/671 (4.6)		30/639 (4.7)			

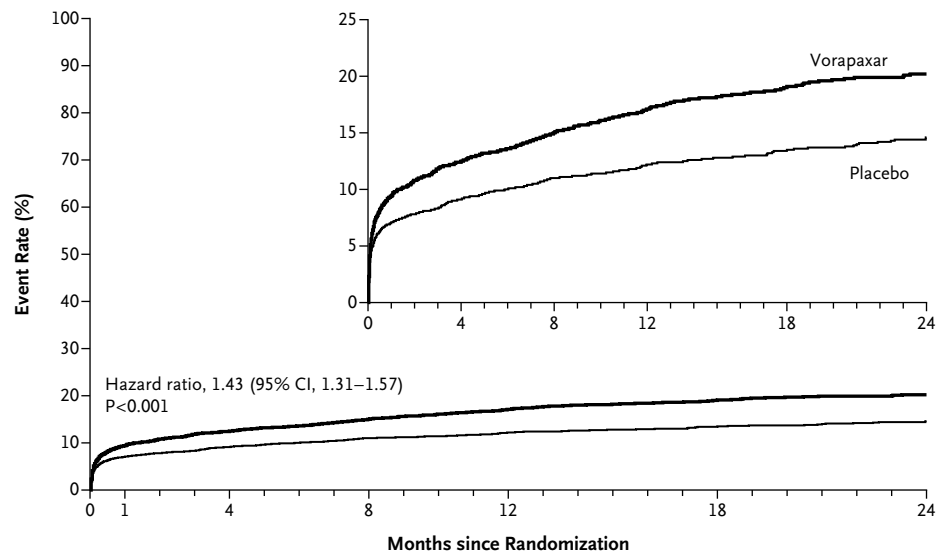
* GUSTO denotes Global Use of Strategies to Open Occluded Coronary Arteries, and TIMI Thrombolysis in Myocardial Infarction.

† Event rates at 2 years were calculated with the use of the Kaplan–Meier method.

‡ The median chest-tube drainage was 308 ml in the placebo group and 350 ml in the vorapaxar group at 8 hours and 580 ml in the placebo group and 635 ml in the vorapaxar group at 24 hours, with total drainage of 780 ml in the placebo group and 830 ml in the vorapaxar group.

A GUSTO Moderate or Severe Bleeding**No. at Risk**

Placebo	6441	5536	5137	4674	3393	1972	650
Vorapaxar	6446	5529	5108	4598	3278	1883	625

B Clinically Significant TIMI Bleeding**No. at Risk**

Placebo	6441	5320	4877	4385	3147	1806	573
Vorapaxar	6446	5257	4772	4219	2950	1663	548

Figure 2. Risk of Bleeding.

Shown are Kaplan–Meier event rates at 2 years in the two study groups for Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria for moderate or severe bleeding (Panel A) and for Thrombolysis in Myocardial Infarction (TIMI) criteria for clinically significant bleeding (Panel B).

(spontaneous) myocardial infarction. These findings support a potential clinical effect of PAR-1 inhibition in reducing thrombosis-mediated coronary events. No effect was observed on stent thrombosis. It is possible that PAR-1 inhibition in addition to dual antiplatelet therapy does not further reduce the risk of stent thrombosis or that other factors are contributory, but additional investigations of PAR-1 inhibition for the prevention of stent thrombosis might be considered. The overall effect of early trial termination, before the planned completion of 1 year of follow-up, is unknown, but the protocol-defined number of primary and secondary end points had been accrued at the time of termination.

In our study, the addition of vorapaxar to standard treatment for patients with acute coronary syndromes significantly increased the occurrence of clinically important bleeding, including intracranial hemorrhage. The magnitude of the increase was not expected on the basis of preclinical and phase 2 data, which suggested that PAR-1 blockade does not increase the risk of bleeding, over and above the risk with aspirin and clopidogrel.^{8-10,18} Rather, the results from our study are consistent with previous evidence indicating that more potent antithrombotic therapy incrementally increases the risk of bleeding.^{3-5,13,19-21} The inhibition of multiple pathways in thrombus formation may be associated with an unacceptable risk of bleeding, even if it offers an improvement in the reduction of ischemic events. In the subgroup of patients who were not receiving a P2Y₁₂ inhibitor at randomization, the hazard of bleeding was not increased, and the observed effect on efficacy tended to be more pronounced. These observations should be considered exploratory, and future studies of vorapaxar in patients not receiving a P2Y₁₂ inhibitor might be considered. A comparison of PAR-1 blockade with P2Y₁₂ inhibition among patients taking aspirin might also be considered. Additional work is needed to understand platelet aggregation in the patients in our study and the interplay between clinical, genomic, or proteomic factors, various biologic pathways, and dose selection.²² It also remains to be determined whether the increase in the rate of intracranial hemorrhage was related to intensive antithrombotic therapy or whether there is a specific link between PAR-1

inhibition and intracranial vascular hemostasis.^{19,23}

The duration of vorapaxar therapy in conjunction with dual antiplatelet therapy may have influenced the risk-benefit profile, since the rate of bleeding continued to increase over time. We studied patients for a much longer period than that in several previous dual antiplatelet trials.³⁻⁵ The progressive accrual of bleeding events with prolonged antiplatelet treatment may alter the long-term balance between efficacy and bleeding and is largely unknown beyond 1 year. Recent trials have also shown a lack of benefit and excessive bleeding with prolonged dual antiplatelet therapy.^{24,25} A better understanding of the clinically beneficial duration of antiplatelet therapies and the well-described but challenging link between bleeding and ischemic events is needed. The second phase 3 study of vorapaxar — the Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events—TIMI 50 trial¹⁵ (NCT00526474) — is currently investigating efficacy and safety in patients with chronic atherosclerotic cardiovascular disease, in whom the use of dual-antiplatelet regimen is typically less common.

In conclusion, vorapaxar, when added to standard therapy with frequent use of aspirin and P2Y₁₂ inhibition, did not significantly reduce the composite end point of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization among patients with acute coronary syndromes without ST-segment elevation. A reduction in the key secondary end point (death from cardiovascular causes, myocardial infarction, or stroke) was observed, but superiority was not declared because a significant reduction in the primary end point was not achieved. Vorapaxar significantly increased bleeding, including major bleeding and intracranial hemorrhage. Future research may lead to a better understanding of whether different strategies of PAR-1 blockade may improve outcomes in patients with coronary artery disease.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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